



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Review

Assessment of ecological hazards and environmental fate of disinfectant quaternary ammonium compounds

Paul C. DeLeo^{a,*}, Carolyn Huynh^b, Mala Pattanayek^b, Katherine Clark Schmid^c, Nathan Pechacek^d

^a Integral Consulting Inc., 200 Harry S. Truman Parkway, Suite 330, Annapolis, MD, 21401, USA

^b Integral Consulting Inc., 545 Sansome Street, Suite 875, San Francisco, CA, 94111, USA

^c Lonza AG, Münchensteinerstrasse 38, 4002, Basel, Switzerland

^d Ecolab Inc., 655 Lone Oak Drive, Mailstop F6, Eagan, MN, 55121, USA



ARTICLE INFO

Keywords:

Quaternary ammonium compounds
Disinfectants
Aquatic ecotoxicity
Biodegradation
Wastewater treatment

ABSTRACT

Disinfectant quaternary ammonium compounds (Quats) have diverse uses in a variety of consumer and commercial products, particularly cleaning products. With the emergence of the COVID-19 pandemic, they have become a primary tool to inactivate the SARS-CoV-2 virus on surfaces. Disinfectant Quats have very low vapor pressure, and following the use phase of the products in which they are found, disposal is typically “down-the-drain” to wastewater treatment systems. Consequently, the potential for the greatest environmental effect is to the aquatic environment, from treated effluent, and potentially to soils, which might be amended with wastewater biosolids. Among the earliest used and still common disinfectant Quats are the alkyl dimethyl benzyl ammonium chloride (ADBAC) compounds and the dialkyl dimethyl ammonium chloride (DDAC) compounds. They are cationic surfactants often found in consumer and commercial surface cleaners. Because of their biocidal properties, disinfectant Quats are heavily regulated for human and environmental safety around the world. Consequently, there is a robust database of information regarding the ecological hazards and environmental fate of ADBAC and DDAC; however, some of the data presented are from unpublished studies that have been submitted to and reviewed by regulatory agencies (i.e., EPA and European Chemicals Agency) to support antimicrobial product registration. We summarize the available environmental fate data and the acute and chronic aquatic ecotoxicity data for freshwater species, including algae, invertebrates, fish, and plants using peer-reviewed literature and unpublished data submitted to and summarized by regulatory agencies. The lower limit of the range of the ecotoxicity data for disinfectant Quats tends to be lower than that for other surface active agents, such as nonionic or anionic surfactants. However, ecotoxicity is mitigated by environmental fate characteristics, the data for which we also summarize, including high biodegradability and a strong tendency to sorb to wastewater biosolids, sediment, and soil. As a result, disinfectant Quats are largely removed during wastewater treatment, and those residues discharged in treated effluent are likely to rapidly bind to suspended solids or sediments, thus mitigating their toxicity.

Abbreviations: ADBAC, alkyl dimethyl benzyl ammonium chloride; ASTER, Assessment Tool for Evaluating Risk, U.S. EPA; BAC, benzalkonium chloride; BPR, Biocidal Products Regulation, Europe; CASRN, Chemical Abstracts Service Registry Number; COVID-19, 2019 novel coronavirus; DDAC, dialkyl dimethyl ammonium chloride; DTDMAC, ditallow dimethyl ammonium chloride; ecoTTC, ecotoxicological threshold of toxicological concern; ECHA, European Chemicals Agency; EPA, United States Environmental Protection Agency; FDA, United States Food and Drug Administration; FFCA, Federal Food, Drug and Cosmetic Act; FIFRA, Federal Insecticide, Fungicide and Rodenticide Act; HESI, Health and Environmental Sciences Institute; MITI, Ministry of International Trade and Industry, Japan; MOA, mode of action; NICNAS, National Industrial Chemical Notification and Assessment Scheme, Australia; OECD, Organisation for Economic Co-operation and Development; PBT, persistent, bioaccumulative, and toxic; PEC, predicted environmental concentration; PNEC, predicted no effect concentration; QSAR, quantitative structure activity relationship; Quats, quaternary ammonium compounds; RED, Reregistration Eligibility Decision; SARS, severe acute respiratory syndrome; SARS-CoV, SARS-associated coronavirus; TEST, Toxicity Estimation Software Tool, U.S. EPA.

* Corresponding author. Integral Consulting Inc., 200 Harry S. Truman Parkway, Suite 330, Annapolis, MD, 21401, USA.

E-mail address: pdeleo@integral-corp.com (P.C. DeLeo).

<https://doi.org/10.1016/j.ecoenv.2020.111116>

Received 6 May 2020; Received in revised form 13 July 2020; Accepted 31 July 2020

Available online 2 September 2020

0147-6513/© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Quaternary ammonium compounds (Quats) are cationic substances that have diverse uses in a variety of consumer and commercial products, such as pesticides, including herbicides and antimicrobial cleaning products (Bureš, 2019). Surface-active Quats have a hydrophilic head that imparts antistatic properties that have made them popular in fabric softeners, antistatic fabric sprays, and hair conditioners (Boethling and Lynch, 1992; Kaj et al., 2014). An additional important function is the natural antimicrobial activity that certain Quats impart. Disinfectant Quats interact with the cytoplasmic membrane of bacteria and yeast, and their membrane surface activity also makes Quats effective against viruses and spores (Gerba, 2015). However, the nonspecific nature of the antimicrobial mechanism of action of disinfectant Quats makes resistance to them unlikely (Gerba, 2015).

Disinfectant Quats have been identified as being effective against Severe Acute Respiratory Syndrome-associated coronavirus (SARS-CoV; Rabenau et al., 2005; Jansen, 2020; Ijaz et al., 2020). The United States Environmental Protection Agency (EPA) has identified Quats among the surface disinfectants for use against SARS-CoV-2, the virus responsible for the 2019 novel coronavirus outbreak, first identified in Wuhan, China (i.e., COVID-19; USEPA, 2020). In addition, benzalkonium chloride is among the active ingredients currently permitted for use as an active ingredient in hand sanitizers in the United States (FDA, 2019). Similarly, in Europe, disinfectant Quats are among the active ingredients for which use in disinfectant products for human hygiene and surface disinfection is under consideration; approval has been granted for use as a wood preservative.

In Europe, antimicrobial agents are regulated as biocides by the European Chemicals Agency (ECHA) under the Biocidal Products Regulation (BPR; European Union Regulation 528/2012). The BPR requires that biocidal products receive an authorization before they can be placed on the market in Europe, which necessitates that all active substances within those products be approved for use. As part of that approval process, ECHA conducts a quantitative estimation of the environmental risk of a substance by comparing compartmental predicted environmental concentrations (PECs) to concentrations at which unacceptable effects on organisms will most likely not occur (aka predicted no effect concentration [PNEC]); this also includes an assessment of food chain accumulation and secondary poisoning (ECHA, 2017). In addition, there is a hazard assessment, which involves the identification of the potential for a substance to persist in the environment (P), accumulate in biota (B), and be toxic (T) combined with an evaluation of sources and major emissions (i.e., a PBT assessment).

The BPR classifies products into 22 biocidal product types for use-specific assessment, grouped in four main areas: disinfectants, preservatives, pest control, and other biocidal products, which include antifouling products and embalming fluids. One notable difference between regulation of antimicrobial products in Europe and the United States is that applied antimicrobial products are regulated in Europe under BPR regardless of whether the product is applied to surfaces, to human skin, or for any other purposes. In the United States, antimicrobial products that are intended for use on humans or animals are regulated as drugs or animal drugs, respectively, by the U.S. Food and Drug Administration under the Federal Food, Drug, and Cosmetic Act, and antimicrobial products intended to control pests on inanimate objects or plants are regulated by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Similar to the BPR, FIFRA-regulated antimicrobial pesticide products must be registered with EPA, which requires that data be provided to demonstrate antimicrobial efficacy and the absence of unreasonable adverse effects to human health and the environment. Among the earliest used disinfectant Quats are the alkyl dimethyl benzyl ammonium chloride (ADBAC) compounds and the dialkyl dimethyl ammonium chloride (DDAC) compounds. ADBAC was first registered as an active antimicrobial ingredient in the United States in 1947 (USEPA, 2006a) and DDAC in 1962 (USEPA,

2006d). The most recently completed review of registration eligibility for ADBAC and DDAC in the U.S. by EPA was in 2006, with the agency specifying the uses that are eligible for reregistration (USEPA, 2006a,d).

For purposes of risk assessment, EPA has grouped Quats into four clusters (USEPA, 1988). The Group I Quat cluster is composed of alkyl or hydroxyalkyl substituted Quats, Group II contains non-halogenated benzyl substituted Quats, Group III consists of di- and tri-chlorobenzyl substituted Quats, and Group IV is made up of Quats with unusual substituents (i.e., charged heterocyclic ammonium compounds). This assessment focuses on the ecological hazards and environmental fate of Group I and Group II Quat clusters, which are frequently used as active ingredients in consumer and commercial antimicrobial products. Group I Quat is dominated by didecyl (C_{10}) dimethyl ammonium chloride (7173-51-5), dioctyl (C_8) dimethyl ammonium chloride (5538-94-3), and mixtures of the two compounds (USEPA, 2006b, Fig. 1A). Group II Quat is composed of 18 unique Chemical Abstracts Service Registry Numbers (CASRNs) (Table 1, Fig. 1B), which were identified in the Reregistration Eligibility Decision (RED) for ADBAC (USEPA, 2006a) and the ADBAC Final Work Plan for Registration Review (USEPA, 2017).

As part of the registration process in the United States and Europe, regulatory agencies solicit submission of ecological toxicity and environmental fate and transport data from manufacturers of antimicrobial active ingredients and formulated antimicrobial products, and from other stakeholders. The majority of submitted studies are unpublished reports that have been prepared by independent laboratories. Key studies used by regulatory agencies for determining product safety adhere to guidelines established by EPA's Office of Pollution Prevention and Toxics and/or by the Organisation for Economic Co-operation and Development (OECD), and are Good Laboratory Practice-compliant. However, submitted study reports typically are not published in peer-reviewed scientific journals, and are presented in a format specifically for regulatory decision-making, which may not be well understood by the public. Consequently, this could lead to the possible misconception that the safety of ADBAC, DDAC, and other Quats have not been adequately assessed. To summarize the regulatory findings in a context that is more consistent with that of the broader scientific community, we conducted an assessment of the ecotoxicological hazards and environmental fate of ADBAC and DDAC using available peer-reviewed literature and publicly available summaries of unpublished data submitted to and reviewed by regulatory agencies.¹ The original study reports cited in those regulatory reviews are not available for public examination. However, it is important to note that those full study reports are provided to competent authorities in Europe (ECHA) and the United States (EPA), which critically review them and incorporate that information into their findings to permit or restrict those chemicals onto the market.

2. Distribution in the environment

As previously noted, the major use pattern of disinfectant Quats in

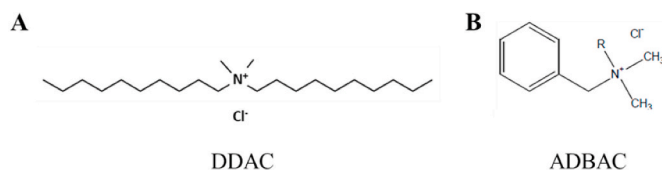


Fig. 1. Chemical structures of (A) C_{10} DDAC (CASRN 7173-51-5) and (B) C_{12} – C_{16} ADBAC (CASRN 68424-85-1), which is a formulation in which R equals alkyl chains of 12 (40%), 14 (50%), or 16 (10%) carbons in length.

¹ The unpublished study reports in the reference list were not available for review. Only summary information as provided in the publicly available regulatory evaluations were assessed.

Table 1
Chemical compounds in the Group II Quat cluster (USEPA, 2006a).

CASRN	Chemical Name	Chain Lengths
121-54-0	Diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride [Benzethonium chloride]	N/A
1330-85-4	Dodecyl benzyl trimethyl ammonium chloride	N/A
139-08-2	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C12 (1%) C14 (98%) C16 (1%)
1399-80-0	Methyl dodecyl benzyl trimethyl ammonium chloride – 80% Methyl dodecyl xylene bis-trimethyl ammonium chloride – 20%	N/A
25155-18-4	Diisobutyl cresoxyethoxyethyl dimethyl benzyl ammonium chloride monohydrate	N/A
53516-75-9	n-Alkyl dimethyl 1-naphthylmethyl ammonium chloride	R = C12 (98%) C14 (2%)
53516-76-0	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C12 (5%) C14 (60%) C16 (30%) C18 (5%)
61789-71-7	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C8-10 (2.5%) C14 (61%) C16 (23%) C18 (2.5%)
63449-41-2	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C8 – Not specified C10 – Not specified C12 (67%) C14 (25%) C16 (7%) C18 – Not specified
68391-01-5	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C12 (67%) C14 (25%) C16 (7%) C18 (1%)
68424-85-1	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C12 (61%) C14 (23%) C16 (11%) C18 (5%) R = C12 (40%) C14 (50%) C16 (10%) R = C12 (25%) C14 (60%) C16 (15%) R = C12 (14%) C14 (58%) C16 (28%) R = C12 (65%) C14 (25%) C16 (10%) R = C12 (3%) C14 (95%) C16 (2%) R = C12 (5%) C14 (90%) C16 (5%) R = C12 (40%) C14 (50%) C16 (10%)
68989-01-5	Alkyl dimethyl benzyl ammonium (ADBA) saccharinate	
73049-75-9	Dialkyl dimethyl benzyl ammonium chloride (BAC)	R = C12 (5%) C14 (60%) C16 (30%) C18 (5%)
8001-54-5	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C12 (50%) C14 (30%) C16 (17%) C18 (3%)
8045-21-4	Alkyl (ethylbenzyl) dimethyl ammonium chloride (ADEBAC)	R = C12 (50%) C14 (30%) C16 (17%) C18 (3%)
85409-22-9	Alkyl dimethyl benzyl ammonium chloride (ADBAC)	R = C12 (70%) C14 (30%)
85409-23-0	Alkyl (ethylbenzyl) dimethyl ammonium chloride (ADEBAC)	R = C12 (68%) C14 (32%)
N/A	n-alkyl dimethyl dimethyl ammonium chloride	R = C12 (68%) C14 (32%)

the United States is as the active antimicrobial ingredient in consumer and institutional cleaning products. Following the use phase of these products, disposal is typically “down-the-drain” to wastewater treatment systems (Boethling and Lynch, 1992). In addition, vapor pressures are extremely low: 3.53×10^{-12} mm Hg (4.7×10^{-10} Pa) for ADBAC (USEPA, 2006a) and 2.33×10^{-11} mm Hg (3.1×10^{-9} Pa) for DDAC (USEPA, 2006d). Therefore, disinfectant Quats are not expected to volatilize significantly from soil or water (Boethling and Lynch, 1992). Consequently, the potential for greatest environmental effect is to the aquatic environment, from treated effluent, and potentially to soils, which might be amended with biosolids from wastewater treatment systems (Fig. 2).

Therefore, the most relevant compartments for the examination of the fate of antimicrobial Quats are centralized wastewater treatment facilities, surface waters, and associated sediments and soils amended with biosolids. Sorption and biodegradation are two mechanisms that greatly affect the fate of disinfectant Quats in various environmental compartments (Zhang et al., 2015). The Quats have strong affinity for sewage sludge, sediments, and soils, and there is evidence of rapid biodegradation in conventional wastewater treatment systems, aquatic systems, and soils.

2.1. Fate in wastewater treatment systems

Boethling and Lynch (1992) observed that removal of Quats from acclimated activated sludge wastewater treatment systems should generally exceed 90% with a high degree of biodegradation. A study submitted in support of the registration of ADBAC in Europe reported a very high level of removal of C₁₂₋₁₆ADBAC in a continuous activated sludge test (OECD 303 A; ECHA, 2015a). Similarly, ECHA (2015b) concluded that DDAC is removed from wastewater at very high percentages (>99.99%), based on data from a continuous activated sludge

test (OECD 303 A), and that the primary mechanism for removal is biodegradation. Clara et al. (2007) observed removal of 98% or greater for C₁₀DDAC and C₁₂₋₁₆ADBAC by municipal wastewater treatment facilities with conventional secondary activated sludge technology in Austria, noting that 80% or greater was removed via biotransformation.

2.2. Sorption

ADBAC and DDAC have a tendency to strongly adsorb to soils due to their cationic charge (ECHA, 2015a,b). Data from adsorption/desorption studies confirm that ADBAC and DDAC are immobile in soil and have high partition coefficients (Table 2a,b).

Because of their strong adsorption to soils, ADBAC and DDAC are not expected to migrate in subsurface environments and have low potential to leach into surface water and groundwater (ECHA, 2015a,b).

2.3. Degradation in the environment

2.3.1. ADBAC

Based on experimental data submitted to support registration in the United States and Europe, ADBAC was found to be hydrolytically stable under abiotic and buffered conditions over the pH range 5–9 (ECHA, 2015a; USEPA, 2006b). ADBAC is also photostable in pH 7 buffered aqueous solutions; however, in the presence of a photosensitizer, ADBAC has been shown to degrade, with a half-life of 7.1 days (USEPA, 2006b).

There are several reliable studies where the aerobic biodegradation of ADBAC was investigated; summaries are provided by TRS (2011). A 28-day Closed Bottle Test (OECD 301D) using a sewage treatment plant inoculum reported between 82% and 85% degradation of ADBAC in 28 days and concluded that ADBAC is ultimately biodegradable (Corby, 1992, as cited in TRS, 2011); that is, complete mineralization of at least

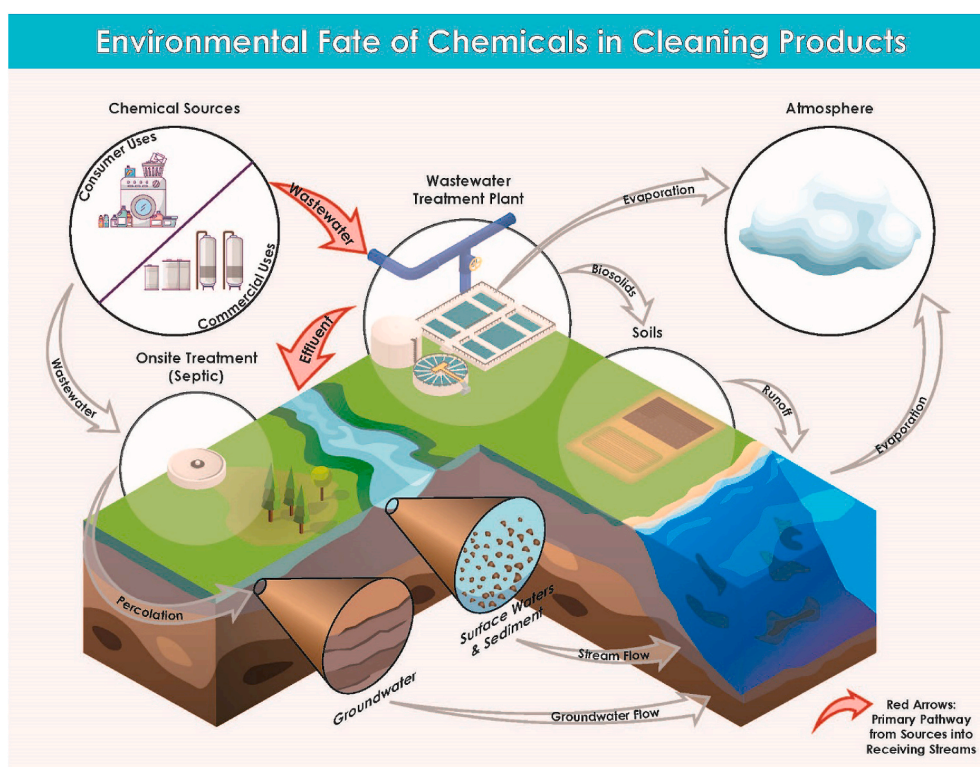


Fig. 2. Primary pathways for entry of antimicrobial Quats to the environment.

Table 2a

Partition coefficients for ADBAC in certain soils and sediments (USEPA, 2006a; ECHA, 2015a).

Soil Type	K _a (adsorption) (L/kg)	K _{oc} (mobility) (L/kg)	K _{des} (desorption) (L/kg)	K _{d,oc} (mobility) (L/kg)
Sand	6172	6,171,657	7173	7,137,310
Loamy sand	1543	16,679	6795	73,459
Sandy loam	5123	640,389	96,540	12,067,457
Loam	630	18,251	2828	81,971
Silt loam	10,797	2,159,346	14,083	2,816,590
Silt loam	2032	812,943	2778	1,111,200
Clay loam	32,429	1,663,039	165,556	8,490,062

Table 2b

Partition coefficients for DDAC in certain soils and sediments (USEPA, 2006d; ECHA, 2015b).

Soil/Sediment Type	K _a (adsorption) (L/kg)	K _{oc} (mobility) (L/kg)	K _{des} (desorption) (L/kg)	K _{d,oc} (mobility) (L/kg)
Sand	1095	437,805	591	236,473
Loamy sand	1787	40,339	2387	53,883
Sandy loam	8179	908,757	2074	230,498
Loam	1456	43,855	2117	63,765
Silt	2188	160,882	3161	232,426
Silty clay loam	32,791	1,599,564	8309	405,328
Silt loam	30,851	1,469,081	7714	367,334
Silt loam	2868	120,000	4237	177,280
Clay soil	9230	280,547	3718	113,009

60% of the test substance to CO₂, biomass, water, and other inorganic substances like NH₃ (OECD, 2006). An aerobic biodegradability study using the CO₂ evolution similar to the OECD 301 B guideline reported 72% of the C₁₂–C₁₈ADBAC had degraded over 28 days (Bazzon and Deschamps, 2002, as cited in TRS, 2011). The authors concluded that the test substance was readily biodegradable; that is, it degrades quickly

(passing the 10-day window requirement) and completely (60–100%) within 28 days (OECD, 2006). Another study following the OECD 301 B guideline reported 95.5% degradation of C₁₂–C₁₈ADBAC in 28 days (Van Dievoet and Bouillon, 2005, as cited in TRS, 2011; ECHA, 2015a). Two studies using the semicontinuous activated sludge test method report very high removal, 94% and 100%. However, it is not clear whether the mechanism of removal was degradation or sorption because CO₂ evolution was not measured and Quats commonly sorb to sewage sludge (Madsen et al., 2001). Van Ginkel (1995) summarized the work of Masuda et al. (1976) studying the biodegradability of individual ADBAC compounds using the Standard MITI test method. Biodegradation rates of 79%–95% were found for C₈, C₁₀, C₁₂ and C₁₄ ADBAC. However, there was virtually no biodegradation of C₁₆ ADBAC (5%) and C₁₈ ADBAC (0%). Van Ginkel attributes the “discrepancies” in biodegradation rates to the inhibitory effect of the quaternary ammonium salts on the inoculum used in the test method.

Mackrell and Walker (1978) proposed several mechanisms of aerobic degradation for Quats including cleavage of the C–N bond followed by β-oxidation of the alkyl side chain; activation of the terminal methyl group by ω-oxidation followed by β-oxidation of the alkyl side chain, and cleavage of the aromatic ring for benzalkonium Quats. Tezel et al. (2012) report biotransformation of ADBAC compounds beginning with cleavage of the C_{alkyl}–N bond and formation of benzyldimethylamine.

ADBAC is not generally found to be degradable under anaerobic conditions. An anaerobic aquatic metabolism study conducted over 12 months reported very little degradation of the radiolabeled ADBAC test substance; mean recovery of the test substance at the end of the study was almost 95% (USEPA, 2006b).

2.3.2. DDAC

Based on experimental data submitted to support registration in the United States and Europe, DDAC was found to be hydrolytically stable under abiotic and buffered conditions over the pH range 5–9 (ECHA, 2015b; USEPA, 2006c). DDAC is also photostable in pH 7 buffered aqueous solutions, even in the presence of a photosensitizer (USEPA,

2006c).

DDAC is generally considered to be biodegradable under aerobic aquatic conditions (Zhang et al., 2015). A number of guideline studies demonstrating the biodegradability of DDAC have been submitted to authorities in Europe and the United States to support its registration (USEPA, 2006c,d; ECHA, 2015b). DDAC meets the criteria for readily biodegradability, with greater than 70% degradation observed in 28 days (Downing, 1993; Schaefer, 1996; Hirshen et al., 1998; Fiebig, 2006, as cited in ECHA, 2015b). The criteria for inherent biodegradability were also satisfied by a study using the OECD 302 B guideline that observed 87%–94% degradation after 28 days (Hirshen et al., 1998, as cited in ECHA, 2015b). One study reporting results for two DDAC test compounds did not meet the 10-day window for readily biodegradability but did show high ultimate biodegradability (>80% in 28 days), suggesting limitations with the implementation of the test procedure (Gledhill, 2006, as cited in USEPA, 2006c). Additional data from an activated sludge die away test showed >90% degradation by virtue of CO₂ evolution (Schaefer, 2001, as cited in ECHA, 2015b).

Nishihara et al. (2000) proposed a biodegradation pathway for DDAC involving an N-dealkylation process that yields decyldimethylamine which is further dealkylated to dimethylamine (DMA). The resultant decanal/decanoic acid and DMA are labile to complete mineralization to CO₂ and water.

Data are very limited regarding potential biodegradation in soil and sediment. One aerobic soil metabolism study found DDAC to be stable, with very little degradation over 365 days (Cranor, 1991, as cited in USEPA, 2006c; ECHA, 2015b). Another study evaluating the potential transformation in aquatic sediments using a method consistent with OECD 308 found that DDAC rapidly partitioned to sediments and was stable in the sediments over the 120-day test period (de Vette et al., 2000, as cited in ECHA, 2015b). Given the robust mineralization observed under the stringent conditions of the ready biodegradation tests and the high removal in sewage treatment plants, this lack of biodegradation, even primary biodegradation, in these studies is surprising. It may be that the aerobic conditions were not maintained in these older tests. Further clarification of the behavior of these substances in soil and sediment according to current environmental fate guidelines is needed.

3. Ecotoxicity

Ecotoxicity studies for ADBAC and DDAC compounds were identified from a variety of sources, including hazard and risk assessments conducted by authoritative agencies. Authoritative documents that were reviewed include 1) the RED for Alkyl Dimethyl Benzyl Ammonium Chloride (USEPA, 2006a); 2) the RED for Aliphatic Alkyl Quaternaries (USEPA, 2006d); 3) the Ecological Risk Assessment in Support of the Antimicrobials Division's Reregistration of ADBAC and DDAC (USEPA, 2006e); 4) the Ecological Hazard and Environmental Risk Assessment Chapter Alkyl Dimethyl Benzyl Ammonium Chloride (USEPA, 2006f); 5) the Directive 98/8/EC Assessment report for ADBAC and DDAC (ECHA, 2015a,b); and 6) the ADBAC Category, High Production Volume (HPV) Chemicals Challenge, Final Test Status and Data Review (TRS, 2011). In addition, we searched the EPA ECOTOXicology knowledgebase database (USEPA, 2019a), the EPA Pesticide Ecotoxicity Database (USEPA, 2019b), and the Health and Environmental Sciences Institute (HESI) EnviroTox Database (HESI, 2019) for ecotoxicity data via CASRN. Data were identified for ADBAC and DDAC compounds listed in Table 3 and were reviewed collectively for each group regardless of CASRN.

Ecotoxicity data for ADBAC compounds are available for 29 freshwater species for various trophic groups, including algae, fish, invertebrates, and aquatic plants. A total of 537 data points were identified stemming from studies investigating acute and chronic toxicity.

Ecotoxicity data for DDAC compounds are available for 16 freshwater species for various trophic groups, including algae, fish, and

Table 3

Data identified for ADBAC and DDAC compounds with the number of data points associated for each CASRN.

Compound	CASRN	Data Points
ADBAC	122-18-9	3
	139-07-1	14
	68,391-01-5	7
	121-54-0	40
	1330-85-4	7
	1399-80-0	19
	25,155-18-4	3
	53,516-76-0	7
	61,789-71-7	6
	63,449-41-2	106
	68,391-01-5	1
	68,424-85-1	122
	8001-54-5	201
	85,409-22-9	1
	7173-51-5	179
	5538-94-3	12
	68,607-28-3	3
DDAC		

invertebrates. A total of 194 data points were identified stemming from studies investigating acute and chronic toxicity.

There are more reported freshwater ecotoxicity data for ADBAC compounds than DDAC compounds. The taxa most commonly used for ADBAC and DDAC compounds, from highest to lowest, are fish > invertebrates > algae > plants, and fish > invertebrates > algae, respectively. Freshwater species vary considerably between studies for each compound. In the assessment review, data are considered acute if they are described as such in the study, if the endpoint is presented as a 50% effective or lethal dose (EC50 or LC50), if the endpoint is presented as a 90% effective dose (EC90), or if exposure duration is equal to or less than the recommended standardized test guideline. Data are considered chronic if they are described as such in the study, or if the endpoint is presented as a lowest-observed-effect-concentration, a no-observed-effect-concentration, a 10% effective concentration (EC10), or an effect that would influence the long-term well-being of a test species (25% reduction in a nonlethal endpoint [IC25]). Acute studies with lethality endpoints in fish are the most abundant sources of data for both ADBAC and DDAC compounds.

There is considerable variability among the freshwater data ranges for acute and chronic trophic groups reviewed in this present study (Fig. 3; Table 4 and Table 5).

The lowest effect concentration ranges are variable for ADBAC and DDAC compounds based on acute and chronic studies and trophic group. For example, the lowest effect concentrations for ADBAC and DDAC compounds observed for algae are similar (as low as 0.014 for acute and 0.001 for chronic). However, ADBAC compounds have a lower observed effect concentration for invertebrates, whereas DDAC compounds have a lower observed effect concentration for fish. The highest effect concentrations are consistently observed in DDAC compounds across all trophic groups (as high as 38,000 mg/L in acute invertebrate studies). It is not clear whether these apparent differences are merely the result of greater testing of ADBAC given the diversity of that chemistry as noted in Table 1.

4. Discussion

Disinfectant Quats have been found to occur in a wide variety of environmental media, including surface waters, sediments, sewage, and sewage sludge (Zhang et al., 2015). Pati and Arnold (2020) recently observed disinfectant Quats at low levels in wastewater effluent (0.4 µg L⁻¹ to 6.6 µg L⁻¹) and sediments downstream from wastewater treatment plant discharges (0.1 µg g⁻¹ to 4.5 µg g⁻¹) in Minnesota (U.S.A). These observations are expected because the life cycle of these compounds typically results in their down-the-drain disposal, and while removal in wastewater treatment plants is high, it will not be complete.

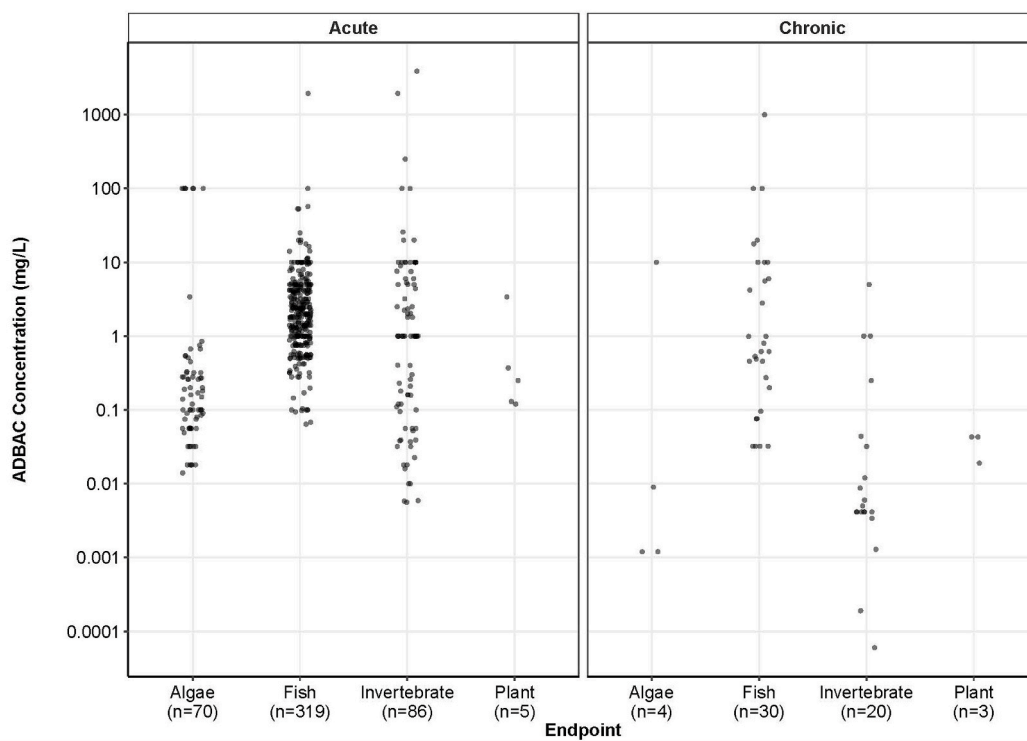
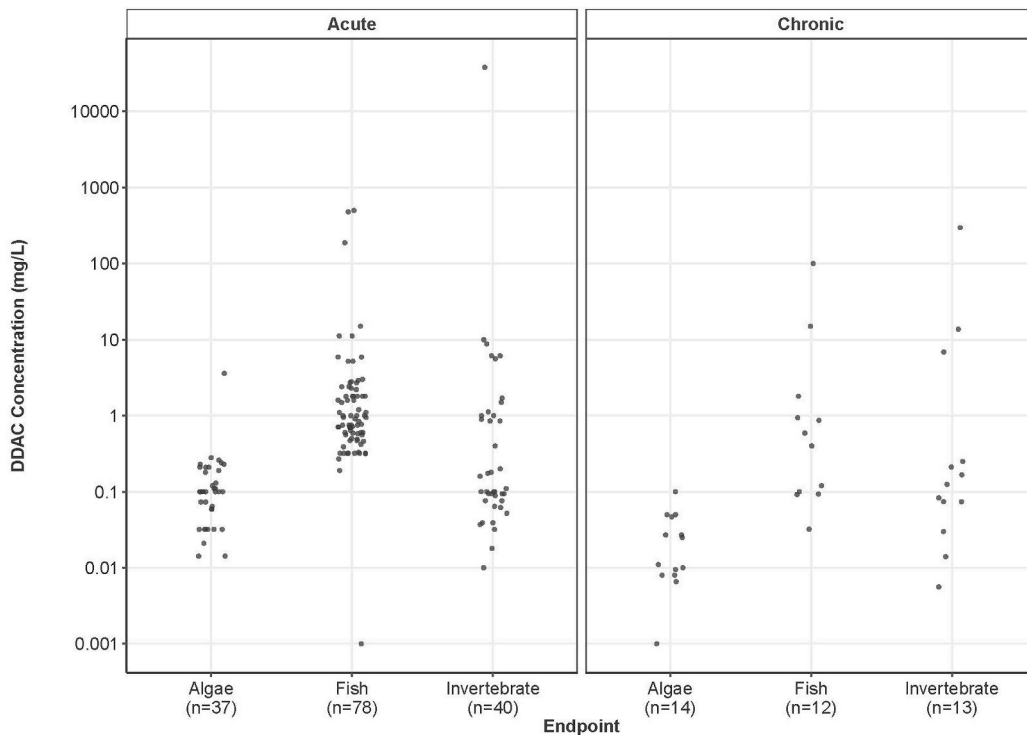
(A)**(B)**

Fig. 3. Comparison of acute and chronic aquatic ecotoxicity data ranges of the disinfectant Quats (A) ADBAC and (B) DDAC from freshwater studies reviewed in the present assessment. Acute endpoints include 50% lethal (effective) concentrations and others (Supplemental Data). Chronic endpoints include lowest-observed-effect concentration, no-observed-effect concentration, 10% lethal concentration, and others (Supplemental Data). Number of freshwater data points used to calculate the mean for each type of study are given below the bars. Data have been logarithmically scaled.

Table 4
Summary of acute and chronic toxicity value ranges for ADBAC compounds.

Trophic Level	Test Type	Concentration Range (mg/L)	Reference
Algae	Acute	0.014–100	1
	Chronic	0.0012–10	
Invertebrate	Acute	0.0056–3880	2
	Chronic	0.00006–5	
Fish	Acute	0.064–1940	3
	Chronic	0.001–17.8	
Plant	Acute	0.12–3.4	4
	Chronic	0.019–0.043	

Notes:1: Canton and Mathijssen-Spiekman (1983); ECHA (2015a); Fitzgerald and Faust (1963); Lusse et al. (1986); Mayer et al. (2001), as cited in TRS (2011); Nyberg (1988); TRS (2011); Utsunomiya et al. (1997); Wong and Wainwright (1994) 2: Canton and Mathijssen-Spiekman (1983); ECHA (2015a); HESI (2019); Huber et al. (1994); Jenkins (2007), as cited in TRS (2011); Lavorgna et al. (2015); Li (2008); Liao and Guo (1990); Liu et al. (2007); McIntyre and Pate (1992), as cited in TRS (2011); Oplinger and Wagner (2009a); Pate and McIntyre (1991), as cited in TRS (2011); TRS (2011); USEPA (2002, 2006f, 2019b); Vallejo-Freire et al. (1954); Waller et al. (1996)3: Applegate et al. (1957); Bills et al. (1993); Bond et al. (1960); Bouck and Johnson (1979); Byrne et al. (1989); Canton and Mathijssen-Spiekman (1983); Ciereszko et al. (2004); Cope (1965); ECHA (2015a); HESI (2019); Holland et al. (1960); Hoskins and Dalziel (1984); Hughes (1973); Jones (1962); Krzeminski et al. (1977); MacPhee and Ruelle (1969); Mayer and Ellersieck (1986); McIntyre and Pate (1992b), as cited in TRS (2011); Oplinger and Wagner (2009b); Pate and McIntyre (1991), as cited in TRS (2011); Rodgers et al. (1951); Rucker (1948); Rucker and Whipple (1951); Surber and Pickering (1962); Sword and Stuermer (1994), as cited in TRS (2011); Tooby et al. (1975); USEPA (2002, 2006a,f); Willford (1966); Wright and Snow (1975)4: Desjardins et al. (2005), as cited in TRS (2011); Vervliet-Scheebaum et al. (2008); Walker and Evans (1978).

Table 5
Summary of acute and chronic toxicity values ranges for DDAC compounds.

Trophic Level	Test Type	Concentration Range (mg/L)	Reference
Algae	Acute	0.0142–3.6	1
	Chronic	0.001–0.1	
Invertebrate	Acute	0.1–38,000	2
	Chronic	0.014–13.75	
Fish	Acute	0.001–500	3
	Chronic	0.0322–15	

Notes: 1: Canton and Mathijssen-Spiekman (1983); ECHA (2015b); HESI (2019); Krueger et al. (2002), as cited in USEPA (2006g); Tatarazako et al. (2002); USEPA (2002, 2006e); Walker and Evans (1978)2: Bargar and Fisher (1997); Canton and Mathijssen-Spiekman (1983); ECHA (2015b); HESI (2019); Farrell et al. (1998); Tatarazako et al. (2002); USEPA (2002, 2006b, 2006e) 3: Bargar and Fisher (1997); Canton and Mathijssen-Spiekman (1983); ECHA (2015b); Farrell et al. (1998); ECHA (2015b); Johnston et al. (1998); Rhodes (2000), as cited in USEPA (2006g); USEPA (2002, 2006d, 2006e, 2019b); Waller et al. (1993).

There is a sizeable database available to consider potential ecotoxicological effects, particularly to freshwater aquatic organisms, including algae, invertebrates, fish, and aquatic plants. For ADBAC, acute aquatic toxicity data range from 0.0056 mg/L (invertebrates) to 3880 mg/L (invertebrates), and chronic toxicity data range from 0.00006 mg/L (invertebrates) to 3880 mg/L (fish). The range of ecotoxicity data for DDAC is a bit broader, with acute aquatic toxicity ranging from 0.001 mg/L (fish) to 38,000 mg/L (invertebrates), and chronic toxicity data ranging from 0.001 mg/L (algae) to 15 mg/L (fish). While the numerical range is broad, as Fig. 3 illustrates, the study results tend to cluster at 1 or 2 orders of magnitude, and there appear to be outliers that expand the range of the data at both the low and high ends.

The lower limit of the range of acute and chronic toxicity for cationic surfactants tends to be lower than that for other nonionic surfactants like alcohol ethoxylates (Belanger et al., 2006), and anionic surfactants such as alkyl sulfates (Könnecker et al., 2011), alkyl ethoxysulfates, and linear alkylbenzene sulfonates (Cowan-Ellsberry et al., 2014). The

exception is long chain alcohols, for which the lower range of chronic aquatic ecotoxicity data is on the same order of magnitude as the disinfectant Quats (Cowan-Ellsberry et al., 2014). Jackson et al. (2016) review the marine ecotoxicity of several anionic, nonionic, and cationic surfactants; the cationic surfactants reviewed were C₁₅₋₁₇ ditallow dimethyl ammonium chloride (DTDMAC) compounds. The authors conclude that the “marine data fall within typical freshwater data ranges, suggesting approximately equal sensitivity to freshwater species.” The acute and chronic marine ecotoxicity data for DTDMAC fell within the range for the other four surfactant classes reviewed (alcohol ethoxylates, alkyl ethoxysulfates, alkyl sulfates, linear alkylbenzene sulfonates).

Gutsell et al. (2015) review data for a number of categories of chemicals to derive ecotoxicological thresholds of toxicological concern (ecoTTCs), including anionic, cationic, and nonionic surfactants. The median ecoTTC for nonionic surfactants was a factor of 14 greater than that for cationic surfactants, and the median ecoTTC for anionic surfactants was a factor of 26 greater than cationic surfactants. Roberts et al. (2013) discuss how cationic surfactants are generally more toxic than predicted by general narcosis or polar narcosis quantitative structure activity relationships (QSARs). They suggest that cationic surfactants can partition into cell membranes more effectively than anionic or nonionic surfactants and are consequently more toxic. Nonetheless, the suggestion is that cationic surfactants impart toxicity through a narcotic (non-specific) mode of action (MOA). Further evidence of the MOA of cationic surfactants can be gathered through the HESI EnviroTox database (Connors et al., 2019; <http://www.envirotoxdatabase.org/>). The database permits a Consensus MOA assessment for compounds for which it has data available (Kienzler et al., 2019). For ADBAC (CASRN 68424-85-1), the EnviroTox database produces a Consensus MOA as narcotic with a confidence score of 1 (lowest). Among the four source MOA approaches used in the Consensus MOA approach are the EPA Toxicity Estimation Software Tool (TEST); EPA Assessment Tool for Evaluating Risk (ASTER); the OASIS MOA, which is currently utilized in the OECD QSAR Toolbox; and the Verhaar classification framework (Verhaar et al., 1992). For ADBAC, the individual results were narcosis (N), unknown/out of domain (U), narcotic amine (N), and class 5 (not possible to classify according to these rules) for TEST, ASTER, OASIS, and Verhaar, respectively (HESI, 2019). The results for DDAC (CASRN 7173-51-5) were very similar—a Consensus MOA as narcotic with a confidence score of 1, and individual results of narcosis (N), unknown/out of domain (U), narcotic amine (N), and class 5 (not possible to classify according to these rules).

Though the antimicrobial nature of disinfectant Quats may appear to be a negative attribute with respect to ecological hazard and risk, there are a number of favorable environmental fate attributes that mitigate those hazards and risks. For one, the high degree of aerobic biodegradability of ADBAC and DDAC, coupled with the strong tendency to sorb to sewage sludge (biosolids), contributes to the high degree of removal in wastewater treatment systems (Clara et al., 2007). Traces of the compounds that might be released to a receiving water body in treated wastewater effluent will partition to sediment and strongly sorb (Zhang et al., 2015). Similarly, disinfectant Quat residues in sewage sludge that may be applied to land will preferentially bind to the soil and may be unavailable to terrestrial organisms. Chen et al. (2014) demonstrated how in experimental systems, C₁₂-BAC can bind to dissolved organic carbon, causing the level of freely available C₁₂-BAC to be greatly reduced, and thus toxicity in the test system is greatly reduced. The authors conclude that the presence of dissolved or particulate matter in the water column can substantially attenuate the actual exposure concentration of cationic surfactants compared to the total extractable concentration of the test material. Likewise, NICNAS (2016a,b) notes that “[l]aboratory-derived toxicity values in clean test waters overestimate toxicity under environmental conditions as quaternary ammonium surfactants sorb to suspended solids and have a tendency to form complexes with anionic surfactants in natural waters (de Oude, 1992). As a result, the bioavailable fraction of quaternary

ammonium surfactants in environmental waters is reduced by up to 95% (Landis et al., 1993). To correct for this reduction in bioavailability under environmental exposure conditions, the measured ecotoxicity endpoints in laboratory tests (generally conducted in clean synthetic test waters) can be multiplied by a maximum mitigation factor of 20 (Landis et al., 1993)."

5. Conclusion

Substantial data are available to characterize the ecotoxicological hazard and environmental fate of disinfectant Quats, particularly ADBAC and DDAC. Disinfectant Quats demonstrate greater aquatic toxicity than other anionic or nonionic surfactants but impart ecotoxicity through a similar non-specific, narcotic MOA. The environmental fate of disinfectant Quats can also be characterized based on a wealth of available data. Though there are significant environmental hazards, those hazards are mitigated as a result of the typical conditions of use in products with a "down-the-drain" disposal. Disinfectant Quats are largely removed from wastewater through biodegradation and sorption to wastewater biosolids, and traces that may be discharged to surface water or soil will bind to sediment or soil and reduce the available exposure concentration to potential receptors. By one estimate, the bioavailable fraction of quaternary ammonium surfactants in environmental waters is reduced by up to 95%. Consequently, numerous regulatory bodies around the world have affirmed the safety of disinfectant Quats under current use conditions, including use as an active antimicrobial ingredient in consumer and commercial cleaning products.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Katherine Clark Schmid is an employee of Lonza AG, a company that manufactures ADBAC and DDAC. Nathan Pechacek is an employee of Ecolab, Inc., a company that uses ADBAC and DDAC in some of its product lines. Ecolab financially supported the Integral authors (Dr. DeLeo, Ms. Huynh, and Ms. Pattanayek) to contribute to the development of this manuscript.

Acknowledgements

The authors would like to thank Michael Freemantle of Lonza, Inc. for his review and valuable comments on this manuscript. In addition, the authors would like to thank Haitian Lu for his role as a catalyst for this project during his time at Lonza.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ecoenv.2020.111116>.

References

- Applegate, V.C., Howell, J.H., Hall, A.E., Smith, M.A., 1957. Toxicity of 4,346 Chemicals to Larval Lampreys and Fishes. U.S. Fish and Wildlife, vol. 207. Federal Government Series. Available at: <https://spo.nmfs.noaa.gov/sites/default/files/legacy-pdfs/SSRF207.pdf> (U.S. Fish and Wildlife Service).
- Bargar, T.A., Fisher, S.W., 1997. Molluscicide acute and sub-chronic toxicity to the three non-target organisms *Hexagenia limbata*, *Ceriodaphnia dubia*, and *Pimephales promelas*, and neutralization of that toxicity by bentonite clay. *Bull. Environ. Contam. Toxicol.* 58 (2), 275–282.
- Bazzon, M., Deschamps, F., 2002. Biotic Degradation: Biodegradability Evaluation in Aqueous Medium: Ultimate Aerobia of the Referenced Compounds, CATIGENE T 50 for Stepan Europe, by INERIS; INERIS Study 506223 (Unpublished). (not seen, as cited in TRS 2011).
- Belanger, S.E., Dorn, P.B., Toy, R., Boeije, G., Marshall, S.J., Wind, T., Van Compennolle, R., Zeller, D., 2006. Aquatic risk assessment of alcohol ethoxylates in North America and Europe. *Ecotox. Environ. Safety* 64 (1), 85–99.
- Bills, T.D., Marking, L.L., Howe, G.E., 1993. Sensitivity of Juvenile Striped Bass to Chemicals Used in Aquaculture. *Resour. Publ.* 192. U.S. Fish and Wildlife Service.
- Boethling, R.S., Lynch, D.G., 1992. Quaternary ammonium surfactants. In: de Oude, N.T. (Ed.), *Detergents. Anthropogenic Compounds*, 3/3F. Springer, Berlin, Heidelberg.
- Bond, C.E., Lewis, R.H., Fryer, J.L., 1960. Toxicity of various herbicidal materials to fishes. In: Tarzwell, C.M. (Ed.), *Biological Problems In Water Pollution*, Trans. 2nd Seminar, April 20–24, 1959, Tech.Rep.W60-3, U.S. Public Health Service. R.A. Taft Sanitary Engineering Center, Cincinnati, OH, pp. 96–101.
- Bouck, G.R., Johnson, D.A., 1979. Medication inhibits tolerance to seawater in coho salmon smolts. *Trans. Am. Fish. Soc.* 108, 63–66.
- Burés, F., 2019. Quaternary ammonium compounds: simple in structure, complex in application. *Top. Curr. Chem.* 377 (3), 14.
- Byrne, P., Speare, D., Ferguson, H.W., 1989. Effects of a cationic detergent on the gills and blood chemistry of rainbow trout *Salmo gairdneri*. *Dis. Aquat. Org.* 6 (3), 185–196.
- Canton, J.H., Mathijssen-Spiekman, E.A.M., 1983. Comparative Short-Term Research with Water-Organisms to Determine the Acute Toxicity of a Number of Biocides. Report No.668115-001. National Institute of Public Health and Environmental Hygiene.
- Chen, Y., Geurts, M., Sjollem, S.B., Kramer, N.I., Hermens, J.L., Droge, S.T., 2014. Acute toxicity of the cationic surfactant C12-benzalkonium in different bioassays: how test design affects bioavailability and effect concentrations. *Environ. Toxicol. Chem.* 33, 606–615. <https://doi.org/10.1002/etc.2465>.
- Ciereszko, A., Babiak, I., Dabrowski, K., 2004. Efficacy of animal anti-fertility compounds against sea lamprey (*Petromyzon marinus*). *Spermatozoa Theriogenology* 61 (6), 1039–1050.
- Clara, M., Scharf, S., Scheffknecht, C., Gans, O., 2007. Occurrence of selected surfactants in untreated and treated sewage. *Water Res.* 41, 4339–4348.
- Connors, K.A., Beasley, A., Barron, M.G., Belanger, S.E., Bonnell, M., Brill, J.L., de Zwart, D., Kienzler, A., Krailler, J., Otter, R., Phillips, J.L., Embry, M.R., 2019. Creation of a curated aquatic toxicology database: EnviroTox. *Environ. Toxicol. Chem.* 38, 1062–1073. <https://doi.org/10.1002/etc.4382>.
- Cope, O.B., 1965. Sport Fishery Investigations. Fish and Wildlife Service Circular 226, Effects of Pesticides on Fish and Wildlife. U.S. Fish and Wildlife Service, Washington, DC, pp. 51–63.
- Corby, J.E., 1992. CO₂ Production Test – Hyamine 3500-80. Report Number 91-066. Roy F. Weston, Inc., Lionville, PA, USA (Unpublished). (not seen, as cited in TRS 2011).
- Cowan-Ellsberry, C., Belanger, S., Dorn, P., Dyer, S., McAvoy, D., Sanderson, H., Versteeg, D., Ferrer, D., Stanton, K., 2014. Environmental safety of the use of major surfactant classes in North America. *Crit. Rev. Environ. Sci. Technol.* 44 (17), 1893–1993.
- Cranor, W., 1991. Aerobic Soil Metabolism of [¹⁴C]Didecylmethylammonium Chloride (¹⁴C-DDAC). Final Report. Lab Project Number 37006. Study prepared by ABC Laboratories. (Unpublished). (not seen, as cited in USEPA 2006c and ECHA 2015b).
- Desjardins, D., McGregor, J.A., Krueger, H.O., 2005. A 7-Day Toxicity Test of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC; 40% C12, 50% C14, 10% C16; CAS RN 68424-85-1) with Duckweed (*Lemna gibba* G3). Study Number 350A-105. Wildlife International, Ltd., Easton, MD, USA (Unpublished). (not seen, as cited in TRS 2011).
- de Oude, N.T. (Ed.), 1992. *Detergents*. Springer-Verlag, Berlin, Germany, p. 406.
- de Vette, H.Q.M., van Asten, J.G., Hanstveit, A.O., 2000. A water/sediment study of didecylmethylammonium chloride (DDAC) using [¹⁴C]-DDAC. TNO Nutrition and Food Research. Delft, The Netherlands. Study No. IMW-99-9048-01 (Unpublished). (not seen, as cited in ECHA 2015b).
- Downing, J.L., 1993. Aerobic Aquatic Biodegradation of Didecylmethylammonium Chloride Using a Shake Flask Test System. Report No. 40687. ABC Labs, Columbia, MO, USA (Unpublished). (not seen, as cited in ECHA 2015b).
- ECHA, 2017. Guidance on the Biocidal Products Regulation: Volume IV Environment - Assessment and Evaluation (Parts B + C). European Chemicals Agency, Helsinki, Finland.
- ECHA, 2015a. Directive 98/8/EC Concerning the Placing Biocidal Products on the Market; Inclusion of Active Substances in Annex I to Directive 98/8/EC. Assessment Report, Alkyl (C12-16) dimethylbenzyl ammonium chloride. European Chemicals Agency, Italy. Available at: http://dissemination.echa.europa.eu/Biocides/ActiveSubstances/0063-08/0063-08_Assessment_Report.pdf (June).
- ECHA, 2015b. Directive 98/8/EC Concerning the Placing Biocidal Products on the Market; Inclusion of Active Substances in Annex I to Directive 98/8/EC. Assessment Report, Didecylmethylammonium chloride. European Chemicals Agency, Italy. Available at: http://dissemination.echa.europa.eu/Biocides/ActiveSubstances/0067-08/0067-08_Assessment_Report.pdf (June).
- Farrell, A.P., Kennedy, C.J., Wood, A., Johnston, B.D., Bennett, W.R., 1998. Acute toxicity of a didecylmethylammonium chloride-based wood preservative, BARDAC 2280, to aquatic species. *Environ. Toxicol. Chem.* 17 (8), 1552–1557.
- FDA, 2019. Final rule: safety and effectiveness of consumer antiseptic rubs; topical antimicrobial drug products for over-the-counter human use. *Fed. Regist.* 84, 14847–14864. April 12, 2019. U.S. Food and Drug Administration.
- Fiebig, S., 2006. Dodigen 1881: Ready Biodegradability: Modified Sturm Test. Dr. U. Noack-Laboratorien, Germany. Study No. AST97952. (Unpublished). (not seen, as cited in ECHA 2015b).
- Fitzgerald, G.P., Faust, S.L., 1963. Bioassay for algicidal versus algistatic chemicals. *Water Sewage Works* 110, 296–298.
- Gledhill, W.E., 2006. BTC® 1010-E and MAKON® NF-5 – Determination of the Biodegradability of a Test Substance Based on OECD Method 301 B (CO₂ Evolution Test). Laboratory Study No. 13039.6128. Study performed by Springborn Smithers Laboratories, Wareham, MA, USA (Unpublished). (not seen, as cited in USEPA 2006c).
- Gerba, C.P., 2015. Quaternary ammonium biocides: efficacy in application. *Appl. Environ. Microbiol.* 81 (2), 464–469.

- Gutsell, S., Hodges, G., Marshall, S., Roberts, J., 2015. Ecotoxicological thresholds—practical application to an industrial inventory. *Environ. Toxicol. Chem.* 34 (4), 935–942.
- HESEI, 2019. EnviroTox Database & Tools. Health and Environmental Sciences Institute. Available, Version 1.2.0. <http://www.envirotoxdatabase.org/>. (Accessed 19 December 2019).
- Hirschen, D.M., Ziemer, M., Seifert, D., 1998. Bardac 22: DOC Die-Away Test OECD 301 A with Pre-adapted Inoculum. Report No. D0094-1. Clariant GmbH, Frankfurt, Germany (Unpublished). (not seen, as cited in ECHA 2015b).
- Holland, G.A., Lasater, J.E., Neumann, E.D., Eldridge, W.E., 1960. Toxic Effects of Organic and Inorganic Pollutants on Young Salmon and Trout. Res. Bull. No. 5. State of Washington Department of Fish, Seattle, WA.
- Hoskins, G.E., Dalziel, F.C., 1984. Survival of chinook fry (*Oncorhynchus tshawytscha*) following exposure to benzalkonium chloride in soft water. *Prog. Fish-Cult.* 46 (2), 98–101.
- Huber, H.C., Ritter, U., Huber, W., Mucke, W., 1994. Photometrische Bestimmung der Zytotoxizität von Chemikalien mit Mikrokulturen von *Tetrahymena pyriformis* und *Pseudomonas aeruginosa*. *Umweltwissenschaften Schadst.* 6 (5), 251–253.
- Hughes, J.S., 1973. Acute toxicity of thirty chemicals to striped bass (*Morone Saxatilis*). *Proc. Western Assoc. State Game Fish Comm.* 53, 399–413 [S.I.: s.n.].
- Ijaz, M.K., Whitehead, K., Srinivasan, V., McKinney, J., Rubino, J.R., Ripley, M., Jones, C., Nims, R.W., Charlesworth, B., 2020. Microbicidal actives with virucidal efficacy against SARS-CoV-2. *Am. J. Infect. Contr.* S0196–6553 (20), 30313–30318. <https://doi.org/10.1016/j.ajic.2020.05.015>. Advance online publication.
- Jackson, M., Eadsforth, C., Schowaneck, D., Delfosse, T., Riddle, A., Budgen, N., 2016. Comprehensive review of several surfactants in marine environments: fate and ecotoxicity. *Environ. Toxicol. Chem.* 35, 1077–1086. <https://doi.org/10.1002/etc.3297>.
- Jansen, K., 2020. How we know disinfectants should kill the COVID-19 coronavirus. *Chem. Eng. News*, March 13, 2020.
- Jenkins, C.A., 2007. N-Alkyl(C12-C16)-N,N-Dimethyl-N-Benzylammonium Chloride (ADBAC) (Supplied as Barquat DM 50): Acute Toxicity to *Daphnia Magna*. Report No. ADB 0037/072526. Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, England (Unpublished). (not seen, as cited in TRS 2011).
- Johnston, B.D., Seubert, J.M., Kennedy, C.J., 1998. Biochemical effects of didecyldimethylammonium chloride (DDAC) exposure and osmoregulatory stress on juvenile coho salmon, *Oncorhynchus kisutch*. *Arch. Environ. Contam. Toxicol.* 34 (3), 275–279.
- Jones, R.O., 1962. Tolerance of the fry of common warm-water fishes to some chemicals employed in fish culture. *Proc. Southeast. Assoc. Game Fish Comm.* 16, 436–445.
- Kaj, L., Wallberg, P., Brorström-Lundén, E., 2014. Quaternary Ammonium Compounds: Analyses in a Nordic Cooperation on Screening. Nordic Council of Ministers, Copenhagen, Denmark.
- Kienzler, A., Connors, K.A., Bonnell, M., Barron, M.G., Beasley, A., Inglis, C.G., Norberg-King, T.J., Martin, T., Sanderson, H., Vallotton, N., Wilson, P., Embry, M.R., 2019. Mode of action classifications in the EnviroTox database: development and implementation of a consensus MOA classification. *Environ. Toxicol. Chem.* 38, 2294–2304. <https://doi.org/10.1002/etc.4531>.
- Könnecker, G., Regelman, J., Belanger, S., Gamon, K., Sedlak, R., 2011. Environmental properties and aquatic hazard assessment of anionic surfactants: physico-chemical, environmental fate and ecotoxicity properties. *Ecotox. Environ. Safety* 74 (6), 1445–1460.
- Krueger, H.O., Desjardins, D., Kendall, T., Vanhoven, R., 2002. BARDAC 2280: A 96-hr Toxicity Test with the Freshwater Alga (*Selenastrum capricornutum*). Wildlife International, Ltd., Easton, MD, USA (Unpublished). (not seen, as cited in USEPA 2006g).
- Krzeminski, S.F., Gilbert, J.T., Ritts, J.A., 1977. A pharmacokinetic model for predicting pesticide residues in fish. *Arch. Environ. Contam. Toxicol.* 5 (2), 157–166.
- Landis, W.G., Hughes, J.S., Lewis, M.A. (Eds.), 1993. *Environmental Toxicology and Risk Assessment*. ASTM STP 1179. American Society for Testing and Materials (ASTM), Philadelphia, PA, 431 pp.
- Lavorgna, M., Russo, C., D'Ambrosia, B., Parrella, A., Isidori, M., 2015. Toxicity and genotoxicity of the quaternary ammonium compound benzalkonium chloride (BAC) using *Daphnia magna* and *Ceriodaphnia dubia* as model systems. *Environ. Pollut.* 210, 34–39, 2016.
- Li, M.H., 2008. Effects of nonionic and ionic surfactants on survival, oxidative stress, and cholinesterase activity of planarian. *Chemosphere* 70 (10), 1796–1803.
- Liao, I.C., Guo, J.J., 1990. Studies on the tolerance of postlarvae of *Penaeus monodon*. In: japonicus, P., semisulcatus, P., penicillatus, P. (Eds.), *Metapenaeus ensis* and *Macrobrachium rosenbergii* to Benzalkonium Chloride, Benzethonium Chloride and Cetylpyridinium Chloride, vol. 10. Council of Agriculture (COA) Fish. Ser. 24, Fish Dis. Res., pp. 95–99 (in Chinese, English abstract).
- Liu, C.H., Yeh, S.P., Hsu, P.Y., Cheng, W., 2007. Peroxinection gene transcription of the giant freshwater prawn *Macrobrachium rosenbergii* under intrinsic, immunostimulant, and chemotherapeutic influences. *Fish Shellfish Immunol.* 22 (4), 408–417.
- Luske, B., Schroeder, D., Soeder, C.J., 1986. The bromothymol-blue test: a simple algal bioassay and its use for herbicide screening. *Arch. Hydrobiol. Suppl.* 73 (1), 147–152.
- MacPhee, C., Ruelle, R., 1969. Lethal effects of 1888 chemicals upon four species of fish from western North America. *Bull. - For. Wildl. Range Exp. Sta.* 3, 112 (University of Idaho).
- Mackrell, J.A., Walker, J.R.L., 1978. The biodegradation of quaternary ammonium compounds. *Int. Biodeterior. Bull.* 14 (3), 77–88.
- Madsen, T., Boyd, H.B., Nylén, D., Pedersen, A.R., Petersen, G.I., Simonsen, F., 2001. Environmental and Health Assessment of Substances in Household Detergents and Cosmetic Detergent Products. Project No. 615. Danish Ministry of the Environment, Environmental Protection Agency, Copenhagen, Denmark.
- Masuda, F., Machida, S., Kanno, M., 1976. Studies on the biodegradability of some cationic surfactants. In: *Proceedings of the VII International Congress on Surface-Active Substances*, vol. 4. USSR national committee on surface active substances, Moscow, pp. 129–138 (not seen, as cited in Van Ginkel, 1995).
- Mayer Jr., F.L., Ellersieck, M.R., 1986. Manual of Acute Toxicity: Interpretation and Data Base for 410 Chemicals and 66 Species of Freshwater Animals. Publication No.160. U.S. Fish and Wildlife Service, Washington, DC, 505 pp.
- Mayer, P., Oldersma, H., Schoonmade, J.A., 2001. Determination of the Effect of Alkyl Dimethylbenzylammonium Chloride (ADBAC) on the Growth of Fresh Water Green Alga *Selenastrum capricornutum* (OECD Guideline No. 201 and EU C.3). Report no. 99-9072-03. TNO Chemistry, Delft, The Netherlands (Unpublished). (not seen, as cited in TRS 2011).
- McIntyre, D.O., Pate, H.O., 1992. Daily Static-Renewal Chronic 21-day Toxicity Test of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) to *Daphnia magna*. Report number SC890056. Battelle Columbus Operations, Columbus, OH, USA (Unpublished). (not seen, as cited in TRS 2011).
- McIntyre, D.O., Pate, H.O., 1992b. Static-renewal Early Life Stage Toxicity Test of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) to Fathead Minnows. Report Number SC890057. Battelle Columbus Operations, Columbus, OH, USA (Unpublished). (not seen, as cited in TRS 2011).
- NICNAS, 2016a. Mono- and di-alkyl quaternary ammonium surfactants: environment tier II assessment, Australian Government, 21 April, 2016. National Industrial Chemicals Notification and Assessment Scheme. Available at: <https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-ii-environment-assessments/mono-and-di-alkyl-quaternary-ammonium-surfactants>. (Accessed 19 December 2019).
- NICNAS, 2016b. Benzalkyl quaternary ammonium surfactants: environment tier II assessment, Australian Government, 01 July 2016. National Industrial Chemicals Notification and Assessment Scheme. Available at: <https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-ii-environment-assessments/benzalkyl-quaternary-ammonium-surfactants>. (Accessed 19 December 2019).
- Nishihara, T., Okamoto, T., Nishiyama, N., 2000. Biodegradation of didecyldimethylammonium chloride by *Pseudomonas fluorescens* TN4 isolated from activated sludge. *J. Appl. Microbiol.* 88, 641–647. <https://doi.org/10.1046/j.1365-2672.2000.01007.x>.
- Nyberg, H., 1988. Growth of *Selenastrum capricornutum* in the presence of synthetic surfactants. *Water Res.* 22 (2), 217–223.
- OECD, 2006. Revised Introduction to the OECD Guidelines for Testing of Chemicals, Section 3, OECD Guidelines for the Testing of Chemicals, Section, vol. 3. OECD Publishing, Paris. <https://doi.org/10.1787/9789264030213-en>.
- Oplinger, R.W., Wagner, E.J., 2009a. New Zealand mudsnail containment: tests of chemicals, copper strips, fluorochrome marking and terrestrial movement. *Interim. J. Sci.* 15 (4), 41–53.
- Oplinger, R.W., Wagner, E.J., 2009b. Toxicity of common aquaculture disinfectants to New Zealand mud snails and mud snail toxicants to rainbow trout eggs. *N. Am. J. Aquacult.* 71 (3), 229–237.
- Pate, H.O., McIntyre, D.O., 1991. Daily Static-Renewal Acute 48-hour Toxicity Test of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) to *Daphnia Magna*. Study Number SC890052. Battelle Columbus Division, Columbus, OH, USA (Unpublished). (not seen, as cited in TRS 2011).
- Pati, S.G., Arnold, W.A., 2020. Comprehensive screening of quaternary ammonium surfactants and ionic liquids in wastewater effluents and lake sediments. *Environ. Sci.: Processes Impacts* 22, 430–441. <https://doi.org/10.1039/C9EM00554D>.
- Rabenau, H.F., Kampf, G., Cinatl, J., Doerr, H.W., 2005. Efficacy of various disinfectants against SARS coronavirus. *J. Hosp. Infect.* 61 (2), 107–111.
- Rhodes, J.E., 2000. Acute Toxicity of P198 to the Rainbow Trout, *Oncorhynchus Mykiss*. In: *Determined under Static Conditions*. ABC Laboratories, Inc. (Unpublished) (not seen, as cited in USEPA 2006g).
- Roberts, D.W., Roberts, J.F., Hodges, G., Gutsell, S., Ward, R.S., Llewellyn, C., 2013. Aquatic toxicity of cationic surfactants to *Daphnia magna*. *SAR QSAR Environ. Res.* 24 (5), 417–427. <https://doi.org/10.1080/1062936X.2013.781538>.
- Rodgers, E.O., Hazen, B.H., Friddle, S.B., Snieszko, S.F., 1951. The toxicity of pyridylmercuric acetate technical (PMA) to Rainbow Trout (*Salmo gairdnerii*). *Prog. Fish-Cult.* 13 (2), 71–73.
- Rucker, R.R., 1948. New compounds for the control of bacterial gill disease. *Prog. Fish-Cult.* 10, 19–22.
- Rucker, R.R., Whipple, W.J., 1951. Effect of bactericides on steelhead trout fry. *Prog. Fish-Cult.* 13, 43–44.
- Schaefer, E.C., 1996. Aerobic Aquatic Biodegradation Test with Didecyldimethylammonium Chloride (DDAC) and a Bentonite Clay: DDAC Complex Conducted with Natural Sediment and Site Water. Project No. 434E-101. Wildlife International Ltd., Easton, MD, USA (Unpublished). (not seen, as cited in ECHA 2015b).
- Schaefer, E.C., 2001. Didecyldimethylammonium Chloride (DDAC): Dieaway in Activated Sludge. Project No. 289E-112. Wildlife International, Inc., Easton, MA, USA (Unpublished). (not seen, as cited in ECHA 2015b).
- Surber, E.W., Pickering, Q.H., 1962. Acute toxicity of endothal, diquat, hyamine, dalapon, and silvex to fish. *Prog. Fish-Cult.* 24 (4), 164–171.
- Sword, M.C., Stuermer, L., 1994. Static-renewal Acute Toxicity of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) to Fathead Minnow (*Pimephales promelas*) in Dilution Water Amended with 20 Mg/l Humic Acid. Report Number 41235. ABC Laboratories, Columbia, MO, USA (Unpublished). (not seen, as cited in TRS 2011).

- Tatarazako, N., Yamamoto, K., Iwasaki, K., 2002. Subacute toxicity of wood preservatives, DDAC and BAAC, in several aquatic organisms. *J. Health Sci.* 48 (4), 359–365.
- Tezel, U., Tandukar, M., Martinez, R.J., Sobocky, P.A., Pavlostathis, S.G., DOI, 2012. Aerobic biotransformation of n-tetradecylbenzyltrimethylammonium chloride by an enriched *Pseudomonas* spp. community. *Environ. Sci. Technol.* 46 (16), 8714–8722. <https://doi.org/10.1021/es300518c>.
- Tooby, T.E., Hursey, P.A., Alabaster, J.S., 1975. The acute toxicity of 102 pesticides and miscellaneous substances to fish. *Chem. Ind. (Lond.)* 21, 523–526.
- TRS, 2011. Alkylmethylbenzylammonium Chloride (ADBAC) Category High Production Volume (HPV) Chemicals Challenge Final Test Status and Data Review. Toxicology Regulatory Services, Inc. See Supplementary File).
- USEPA, 1988. PR Notice 88-2. Clustering of Quaternary Ammonium Compounds. U.S. Environmental Protection Agency. Available at: <https://www.epa.gov/pesticide-registration/prn-88-2-clustering-quaternary-ammonium-compounds>.
- USEPA, 2002. ECOTOX User Guide: ECOTOXicology Database. U.S. Environmental Protection Agency, Washington, DC, version 3.0. www.epa.gov/ecotox.
- USEPA, 2006a. Reregistration Eligibility Decision (RED) for Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC). EPA739-R-06-009. U.S. Environmental Protection Agency.
- USEPA, 2006b. Environmental Fate Assessment for Alkyl* Dimethyl Benzyl Ammonium Chloride (50% C14, 40% C12, 10% C16) (ADBAC) for the Reregistration Eligibility Decision (RED) Document. Memorandum Dated July 27, 2006. U.S. Environmental Protection Agency.
- USEPA, 2006c. Environmental Fate Assessment of Didecyl Dimethyl Ammonium Chloride (DDAC) for the Reregistration Eligibility Decision (RED) Document. Memorandum Dated July 31, 2006. U.S. Environmental Protection Agency.
- USEPA, 2006d. Reregistration Eligibility Decision for Aliphatic Alkyl Quaternaries (DDAC). EPA739-R-06-008. U.S. Environmental Protection Agency, Washington, DC, August.
- USEPA, 2006e. Ecological Risk Assessment in Support of the Antimicrobials Division's Reregistration of ADBAC and DDAC. U.S. Environmental Protection Agency, Washington, DC, February 3. Available at: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2006-0339-0023>.
- USEPA, 2006f. Ecological Hazard and Environmental Risk Assessment Chapter, Alkyl Dimethyl Benzyl Ammonium Chloride. U.S. Environmental Protection Agency, Washington, DC, August 2. Available at: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2006-0339-0021>.
- USEPA, 2006g. Environmental Effects Assessment of Didecyl Dimethyl Ammonium Chloride (DDAC) for the Reregistration Eligibility Decision (RED) Document. U.S. Environmental Protection Agency, Washington, DC, August 2. Available at: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2006-0338-0022>.
- USEPA, 2017. Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Final Work Plan. U.S. Environmental Protection Agency. Registration Review: Initial Docket Case Number 0350. EPA-HQ-OPP-2015-0737.
- USEPA, 2019a. ECOTOX User Guide: ECOTOXicology Knowledgebase System. U.S. Environmental Protection Agency, Version 5.0. <https://www.epa.gov/ecotox/>. (Accessed 11 November 2019).
- USEPA, 2019b. OPP Pesticide Ecotoxicity Database. U.S. Environmental Protection Agency, Environmental Fate and Effects Division, Washington, DC. Available. <https://ecotox.ipmcenters.org/>. (Accessed 11 November 2019).
- USEPA, 2020. List N: disinfectants for use against SARS-CoV-2. Environmental Protection Agency, Washington, DC. Available at: <https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2>. U.S.
- Utsunomiya, A., Watanuki, T., Matsushita, K., Tomita, I., 1997. Toxic effects of linear alkylbenzene sulfonate, quaternary alkylammonium chloride and their complexes on *Dunaliella* sp. and *Chlorella pyrenoidosa*. *Environ. Toxicol. Chem.* 16 (6), 1247–1254.
- Vallejo-Freire, A., Fonseca Ribeiro, O., Fonseca Ribeiro, I., 1954. Quaternary ammonium compounds as molluscicides. *Science* 119 (3093), 470–472.
- Van Dievoet, F., Bouillon, V., 2005. Biodegradability Test Report According to OECD 301 B – Modified. Report No. ST49132.01.01, dated January 19, 2004 for Stephan Europe, Voreppe, France; from BfB Oil Research S.A., Gembloux, Belgium (Unpublished). (not seen, as cited in TRS 2011 and ECHA 2015a).
- Van Ginkel, C.G., 1995. Biodegradability of cationic surfactants. In: Karsa, D.R., Porter, M.R. (Eds.), *Biodegradability of Surfactants*. Chapman & Hall, London, UK, pp. 183–203.
- Verhaar, H.J.M., Van Leeuwen, C.J., Hermens, J.L.M., 1992. Classifying environmental pollutants. *Chemosphere* 25, 471–491.
- Vervliet-Scheebaum, M., Ritzenthaler, R., Normann, J., Wagner, E., 2008. Short-term effects of benzalkonium chloride and atrazine on *Elodea canadensis* using a miniaturised microbio reactor system for an online monitoring of physiologic parameters. *Ecotoxicol. Environ. Saf.* 69 (2), 254–262.
- Walker, J.R.L., Evans, S., 1978. Effect of quaternary ammonium compounds on some aquatic plants. *Mar. Pollut. Bull.* 9 (5), 136–137.
- Waller, D.L., Rach, J.J., Cope, W.G., Marking, L.L., Fisher, S.W., Dabrowska, H., 1993. Toxicity of candidate molluscicides to zebra mussels (*Dreissena polymorpha*) and selected nontarget organisms. *J. Great Lake. Res.* 19 (4), 695–702.
- Waller, D.L., Fisher, S.W., Dabrowska, H., 1996. Prevention of zebra mussel infestation and dispersal during aquaculture operations. *Prog. Fish-Cult.* 58 (2), 77–84.
- Willford, W.A., 1966. Toxicity of 22 Therapeutic Compounds to Six Fishes. Invest. Fish Control No. 18. U.S. Fish and Wildlife Service.
- Wong, S.L., Wainwright, J.F., 1994. Interpretation of ultrastructural changes in *Cladophora glomerata* resulting from hyamine toxicity. *Bull. Environ. Contam. Toxicol.* 52 (3), 325–332.
- Wright, L.D., Snow, J.R., 1975. The effect of six chemicals for disinfection of largemouth bass eggs. *Prog. Fish-Cult.* 37 (4), 213–217.
- Zhang, C., Cui, F., Zeng, G., Jiang, N., Yang, Z., Yu, Z., Zhu, M., Shen, L., 2015. Quaternary ammonium compounds (QACs): a review on occurrence, fate and toxicity in the environment. *Sci. Total Environ.* 518–519, 352–362.